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DOI 10.1016/j.ctim.2021.102692
ISSN 0965-2299

Publisher: Elsevier

Complementary Therapies in Medicine 59 (2021) 102692

Contents lists available at ScienceDirect

Complementary Therapies in Medicine

journal homepage: www.elsevier.com/locate/ctim

Soy intake is associated with lowering blood pressure in adults: A systematic review and meta-analysis of randomized double-blind placebo-controlled trials

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ARTICLE INFO

Keywords:
Soy
Blood pressure
Hypertension
Review
Meta-analysis

ABSTRACT

Background: Soy has several beneficial effects on cardiovascular disease (CVD); however, results of clinical trial studies are equivocal. Thus, the present study sought to discern the efficacy of soy intake on blood pressure.
Methods: The search process was conducted in PubMed, Scopus, Web of Science, and Cochrane Library, to ascertain studies investigating the efficacy of soy intake on blood pressure in adults, published up to June 2020. A random-effects model was applied to pool mean difference and 95 % confidence interval (CI). Begg's and Egger's methods were conducted to assess publication bias.
Results: Pooled effects from 17 effect sizes revealed a significant improvement in systolic blood pressure (SBP) (−1.70; −3.34 to −0.06 mmHg; I^2 = 45.4 %) and diastolic blood pressure (DBP) (−1.27; −2.36 to −0.19 mmHg, I^2 = 43.9 %) following soy consumption, in comparison with controls. Subgroup analysis demonstrated a reduction in both SBP and DBP in younger participants with lower baseline DBP and intervention durations of <16 weeks.
Conclusion: Our results suggest that soy intake is associated with an ameliorating effect on blood pressure in adults.

1. Introduction

Soy is a traditional food that is globally popular, especially in Asia, and is widely used to produce various food products, such as soybean oil, soy milk, soy flour, and many retail food products.[1] Utilizing soy products in the food processing industry makes it possible to achieve significant economic effects by reducing production costs and standardizing quality.[2,3] Soybean contains compounds such as protein, fiber, vitamins, minerals, and phytochemicals, which has led to considerable research interest regarding its effects on various diseases.[1,4] Accordingly, previous studies have reported protective features of soy in diabetes, cancer, osteoporosis, and menopausal problems,[3] with further studies confirming its beneficial effects on cardiovascular disease (CVD).[5]

One of the most important risk factors of CVD is hypertension, which represents one of the most prevalent non-communicable diseases, worldwide.[6] Several strategies, including medication and lifestyle

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https://doi.org/10.1016/j.ctim.2021.102692
Received 17 January 2021; Accepted 20 February 2021
Available online 24 February 2021

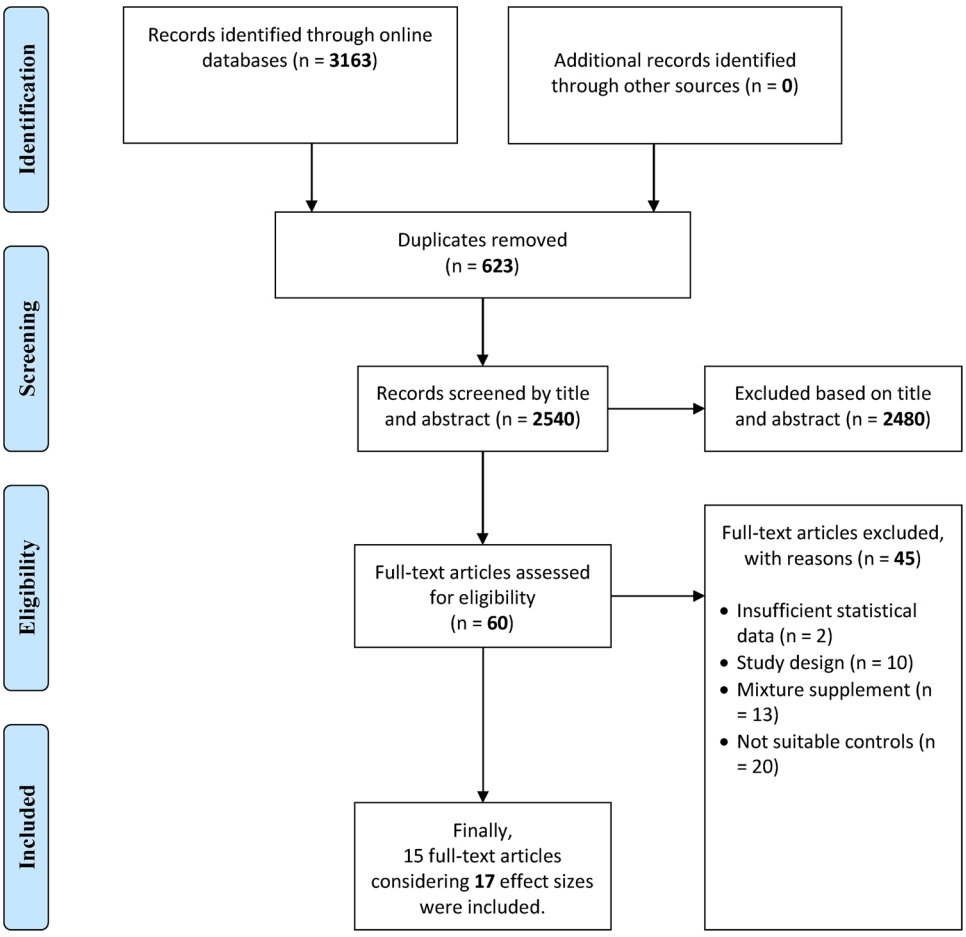

Fig. 1. The process of study selection.

modification are recommended to manage the disorder,[7] whilst numerous studies have been performed to investigate the effects of nutrients on blood pressure.[8] For instance, the Dietary Approaches to Stop Hypertension (DASH) diet has been advocated as part of the treatment protocol for hypertensive patients.[9] Moreover, there are several studies demonstrating the effectiveness of macronutrients on blood pressure.[10,11] In the case of total protein intake, however, the results manifest in the literature are contradictory, although the positive effect of plant based protein on blood pressure has been confirmed.[12] In addition, although observational studies [13,14] have confirmed the efficacy of soy as a vegetable protein on blood pressure, the results of clinical trial studies are equivocal.[15,16]

Due to the limited number of participants in previous clinical trial studies,[17,18] as well as differences in intervention duration,[19,20] age,[21,22] and baseline blood pressure,[18,21,23] it is not possible to draw any firm conclusion regarding the effect of soy on blood pressure. Therefore, in this study we aimed to identify the effect of soy intake on blood pressure by performing a systematic review and meta-analysis of randomized clinical trials.

2. Methods

We undertook our study in accordance with guidelines proposed by the *Preferred Reporting Items for Systematic reviews and Meta-Analyses* (PRISMA).[24] The review protocol was registered with PROSPERO (CRD42020214728).

2.1. Search process

To identify relevant papers investigating the effect of soy on blood pressure, we undertook a systematic search in PubMed, Embase, Scopus, Web of Science, and Cochrane Library, for all available publications up to June 2020, using a combination the relevant terms in titles and abstracts, without making any restrictions (Supplementary material 1). In some cases, we used the wildcard term "*" to increase sensitivity and checked the reference lists of the relevant reviews and Google Scholar to supplement the database search strategy, which was prepared with in-group consensus. After loading retrieved records into EndNote, duplicates were removed.

2.2. Inclusion and exclusion criteria

Four authors independently assessed the records retrieved from the database search. Randomized controlled trials (RCTs) investigating the association of soy intake and blood pressure in adults ($\geq$ 18 years of age) were identified for inclusion. To maximize methodological rigor, only double-blind placebo-controlled trials were then shortlisted for inclusion, to increase quality of evidence, and reduce potential bias in the meta-analysis. Review articles, dissertations, brief reports, observation-designed and non-English language studies were excluded, as were those lacking clinical information or statistical data required for analysis (e.g. baseline of blood pressure, standard deviation (SD), standard error (SE), 95 % confidence intervals (CIs) and interquartile (IQR)). Disagreements in the inclusion or exclusion of any study were resolved by group discussion. For example, one study did not clearly mention term "placebo"

Table 1
Characteristics of the included RCTs.

Study	Country	Type of study	Population	Age group (C vs. I)	Body weight (C vs. I)	BMI (C vs. I)	Intervention type	Sample size	Duration (weeks)	Baseline SBP (mmHg)	Baseline DBP (mmHg)
Teede (2001)	Australia	Randomized, double-blind, placebo-controlled trial	Men and Postmenopausal Women	60 vs. 61	74 vs. 72	26 vs. 25	Soy protein	179	12	130	76
Sagara (2004)	Scotland	Randomized, double-blind, placebo-controlled trial	Hypercholesterolemic and / or hypertensive	52.2 vs. 52.2	83.8 vs. 85.1	27.2 vs. 27.6	Soy protein	50	5	142	87.1
He (2005)	China	Randomized, double-blind, controlled trial.	Healthy	51.4 vs. 50.8	70.6 vs. 70	26.8 vs. 26.9	Soybean protein	276	12	134.7	84.7
Kim (2005)	Korea	Randomized, double-blind, placebo-controlled trial	T2DM	61.7 vs. 59.9	61.1 vs. 64.1	23.8 vs. 24.4	Soybean	30	13	137.5	86.6
Hermansen (2005)	Denmark	Randomized, double-blind, placebo-controlled trial	Hypercholesterolemic	58 vs. 60.6	75.3 vs. 77.1	25.6 vs. 26.4	Soy protein	100	24	133	80.2
Aubertin-Leheudre (2008)	Canada	Randomized, double-blind, placebo-controlled trial	Obese Postmenopausal Women	57.7 vs. 57.1	82.5 vs. 79.6	32.8 vs. 31.2	Soy isoflavone	39	25	125.1	79
Chan (2008)	China	Randomized, double-blind, placebo-controlled trial	Ischaemic stroke	65.8 vs. 66.8	NR*	25 vs. 26.2	Soy isoflavone	102	12	141	77
Kwak (2010)	Korea	Randomized, double-blind, placebo-controlled trial	Prediabetes and newly diagnosed T2DM	57.6 vs. 56.8	65.8 vs. 62.6	24.8 vs. 24.1	Black soy peptide	42	12	125.1	73.6
Wong (2012)	Netherlands	Randomized, double-blind, placebo-controlled trial	Menopausal women with high or normal blood pressure	55.5 vs. 55.8	68.9 vs. 67.6	25.4 vs. 25.3	Soy hypocotyl isoflavones	24	6	140.1	82.8
Liu 1 (2013)	China	Randomized, double-blind, placebo-controlled trial	Postmenopausal women with mild hyperglycemia	54.8 vs. 54.3	54.4 vs.56.1	22.6 vs. 23.6	Soy protein and isoflavones	180	25	127.9	77
Liu 2 (2013)	China	Randomized, double-blind, placebo-controlled trial	Postmenopausal women with mild hyperglycemia	54.8 vs. 56.3	54.4 vs. 56.8	22.6 vs.23.9	Soy isoflavones	180	25	125.9	78.2
Kim (2013)	Korea	Randomized, double-blind, placebo-controlled trial	Postmenopausal women	53.5 vs. 53.7	56.5 vs. 57.7	23.3 vs. 23.2	Soy isoflavone	85	12	116.1	74.6
Squadrito (2013)	Italy	Randomized, double-blind, placebo-controlled trial	Postmenopausal women with metabolic syndrome	55.4 vs. 55.6	NR	31.8 vs. 31.8	Soy isoflavone	108	51	135.7	78.7
Cheng (2013)	Taiwan	Randomized, double-blind, placebo-controlled trial	Healthy postmenopausal women	56.1 vs. 57	55.1 vs. 55.1	22.9 vs. 23.1	Soy isoflavone	82	52	119	77.3
Husain (2015)	Iran	Randomized, double-blind, placebo-controlled trial	Postmenopausal women	50.32 vs. 50.93	NR	NR	Soy	61	8	125.77	81.77
Liu 1 (2015)	China	Randomized, double-blind, placebo-controlled trial	Postmenopausal women with prehypertension	58.5 vs. 57.6	57.6 vs. 56.5	NR	Soy	180	24	130.7	81.6
Liu 2 (2015)	China	Randomized, double-blind, placebo-controlled trial	Postmenopausal women with prehypertension	58.5 vs. 57.7	57.6 vs. 56.5	NR	Soy isoflavone	180	24	131.9	81.6

C (control group); I (intervention group); BMI (body mass index); T2DM (type 2 diabetes mellitus), NR (not reported).

Table 2
The methodological quality of included RCTs on effect of soy intake on blood pressure based on review authors' judgments about each risk of bias item for each included study.

Study	Sequence generation	Allocation concealment	Blinding	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Teede (2001)	+	+	+	?	?	+	+
Sagara (2004)	+	+	+	?	?	+	+
He (2005)	+	?	+	+	+	+	+
Kim (2005)	+	?	+	+	+	+	?
Hermansen (2005)	+	+	+	+	?	+	+
Aubertin-Leheudre (2008)	+	+	+	+	+	+	?
Chan (2008)	+	+	+	+	+	+	+
Kwak (2010)	+	?	+	+	−	+	+
Wong (2012)	+	+	+	?	+	+	+
Liu (2013)	+	?	+	+	+	+	?
Kim (2013)	+	+	+	?	+	+	+
Squadrito (2013)	+	+	+	+	+	+	+
Cheng (2013)	+	+	+	+	−	+	+
Husain (2015)	+	?	+	?	+	+	+
Liu (2015)	+	?	+	+	+	?	+

as the control,[21] however, the study-design was comparable to a placebo-controlled design. Following discussion with clinical and statistical experts, this study was included. In addition, studies were excluded if the control group was not clinically comparable with the intervention, and therefore inclusion would have biased the results. Trials that prescribed effective nutrients, diet, medicines, or other combinations concomitant to soy, in comparison with controls were also excluded.

2.3. Data extraction

After identifying studies for inclusion, a combination of four authors extracted clinical and statistical data, including: first authors last name, corresponding author's e-mail, publication year, country, population, participants' characteristics, intervention and control type, dose and type of supplement, treatment duration, sample size, methodological quality, mean change of interested outcome from baseline at the end of trial, related SD, SE, 95 % CI or IQR. Where required appropriate transformations were undertaken to calculate the SD from studies reporting: SE ($SD = SE \times \sqrt{n}$), 95 % CI ($SD = \sqrt{n} \times (upper\ limit - lower\ limit) / 3.92$) or IQR (SD = IQR / 1.35).[25] In addition, WebPlotDigitizer (https://automeris.io/WebPlotDigitizer) was used to derive the mean change and the corresponding SD when the data were plotted, but not reported. In the case of an article with two different intervention groups and one control group, the intervention groups were considered as different studies, and to avoid giving more weight to them; number of participants in the control group was divided by 2.

2.4. Quality appraisal

Two authors independently assessed quality in the included studies using the Cochrane Collaboration risk of bias assessment tool,[26] which is scored across seven domains being: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other sources of bias. Each included study also received an overall grading of Good (> 2 low risk domains), Fair (= 2 low risk domains), or Poor (< 2 low risk domains).

2.5. Statistical analysis

Weighted mean difference (WMD) and 95 % CI was calculated in Stata v.13, applying a random-effects method. Inter-study heterogeneity was evaluated by checking I^2 index (low: <50%, hight: >50%).[27] Subgroup analyses were planned by effective clinical covariates i.e. age (> 56, < 56 years old), baseline blood pressure (SBP: > 130, < 130 mmHg; DBP: > 80, < 80 mmHg), and intervention duration (< 16, > 16 weeks).

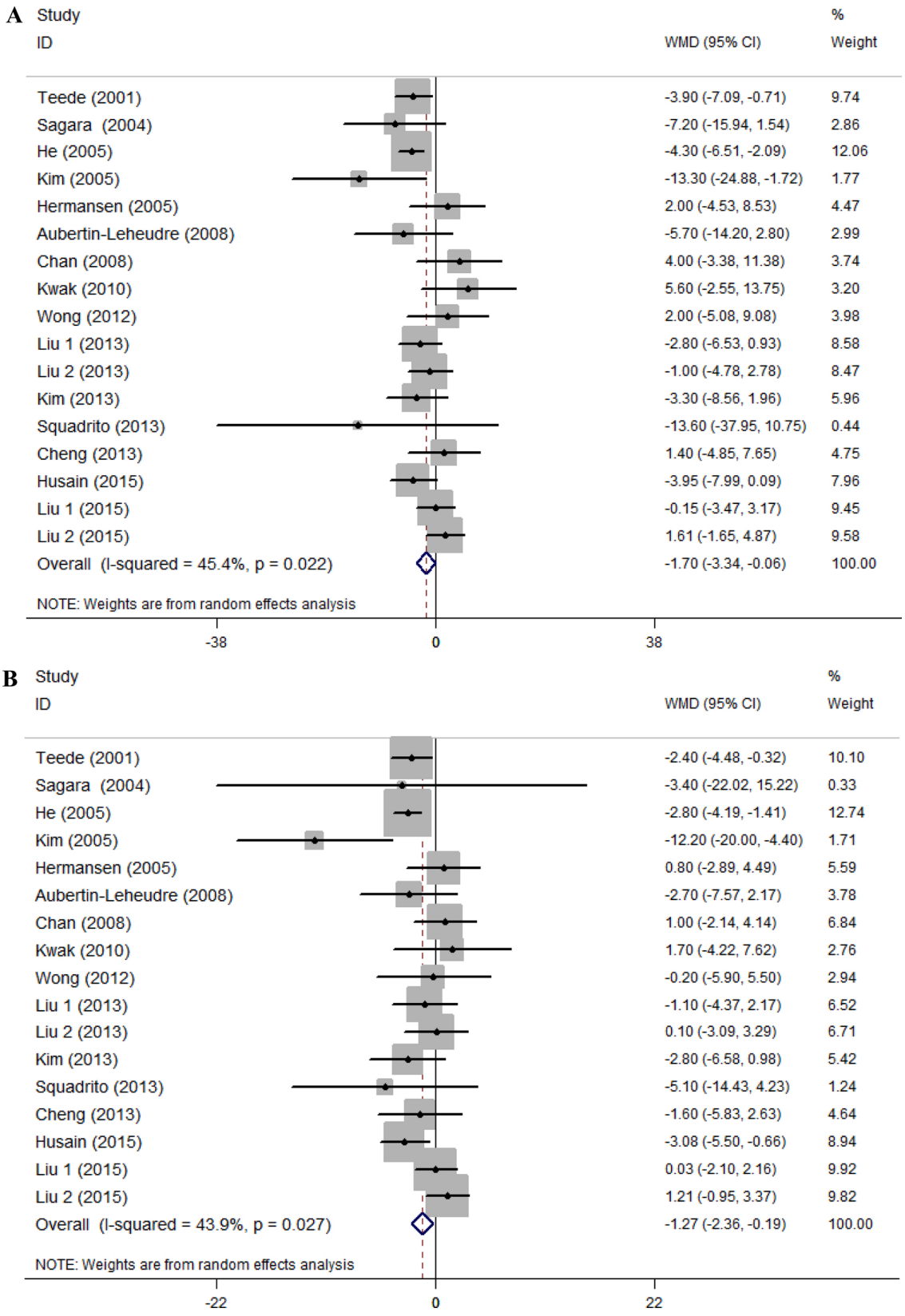

Fig. 2. Forest plot detailing WMDs and 95 % CIs for the meta-analyses of SBP (A) and DBP (B).

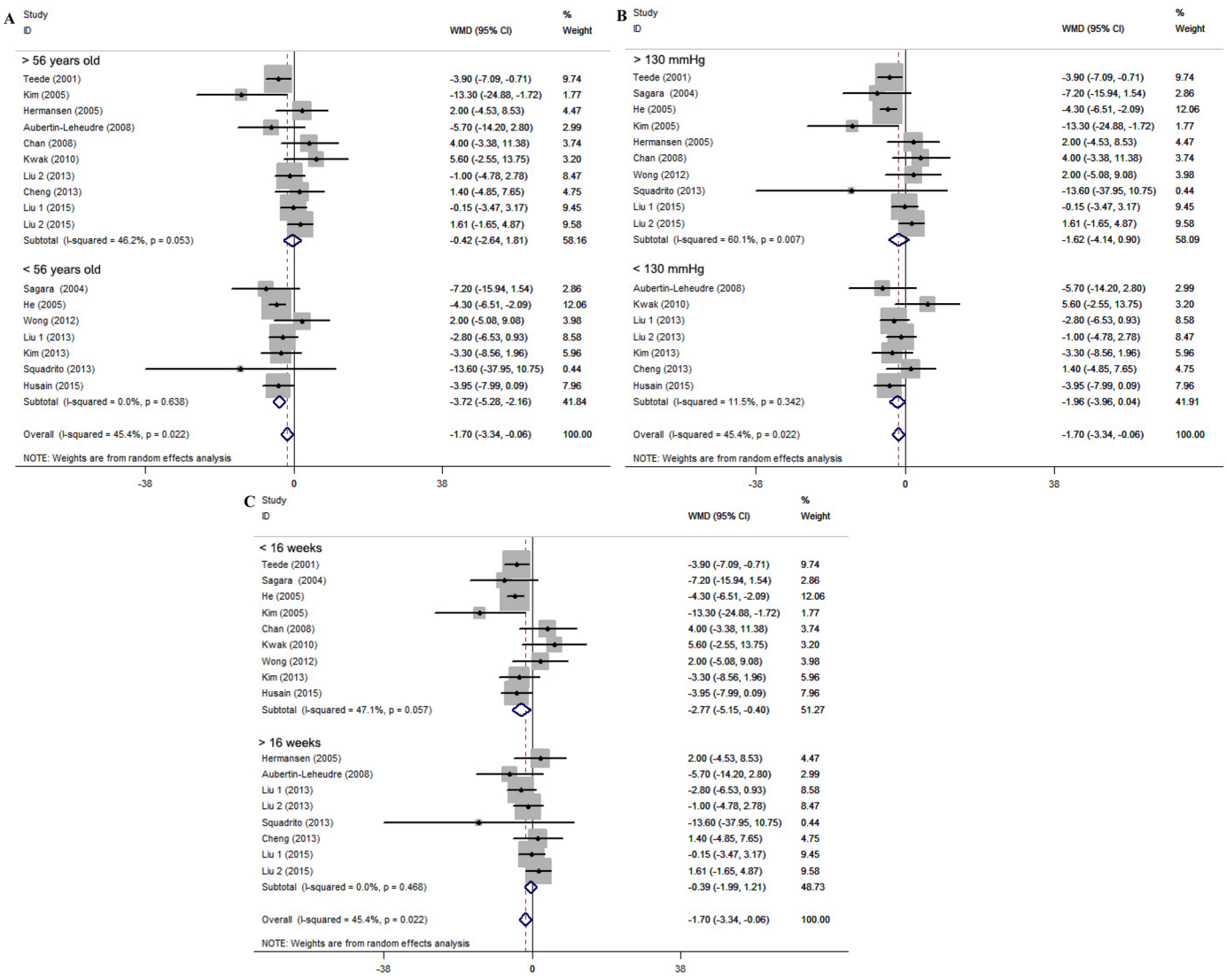

Fig. 3. Findings from subgroup analysis based on age (< 56, > 56 years old) (A), baseline blood pressure (< 130, > 130 mmHg) (B), duration (< 16, > 16 weeks) (C) and region (Asia, Europe, America) (D) regarding the effect of soy consumption on SBP.

Mean changes and their SDs of relevant outcomes were obtained by using the following equations: [mean-post – mean-baseline] and $[(\sqrt{([(SD\ pre)^2 + (SD\ post)^2] - [2\ r \times SD\ pre \times SD\ post])})]$,[28,49,50] respectively. In addition, a sensitivity analysis was applied by discarding each trial in turn, to ensure robustness of results. A Begg's rank-correlation [29] and Egger's regression asymmetry[30] were performed to evaluate potential publication bias. *P*-values of less than 0.05 represented statistical significance.

3. Results

3.1. Results of the search and study characteristics

From 3163 records, 15 RCTs with 17 effect sizes were identified for inclusion, all of which were able to be included in the meta-analysis (Fig. 1). These studies were published between 2001 and 2015. Ten were conducted in Asia,[17,19,20,21,22,31,32,33,34,35] four in Europe,[18,23,36,37] and another one in the United States of America.[38] Participant age ranged from 50.32–66.8 years. Intervention durations were less than 16 weeks [17,18,20,21,22,23,31,32,33] or more than 16 weeks[19,34,35,36,37,38] in nine and six trials, respectively (Table 1).

Baseline blood pressure across studies was reported as SBP < 130 mmHg [17,20,33,34,35,38] and > 130 mmHg [18,19,21,22,23,31,32,36,37] in six and nine RCTs, respectively. In addition, enrolled participants of seven and eight studies had > 80 mmHg [18,19,20,21,23,32,36] and < 80 mmHg [17,22,31,33,34,35,37] DBP, respectively.

3.2. Quality assessment for included studies

Results of the quality assessment are shown in Table 2. Overall, study quality was assessed as good, with a low risk of bias the dominant classification across all domains. All studies were assessed as having low risk of bias for sequence generation and blinding of participants. Six studies were assessed as having unclear risk of bias for allocation concealment, five had unclear risk for blinding of outcome assessment, one had unclear risk for selective reporting and three had unclear risk for other potential sources of bias. Two studies were assessed as having high risk of bias for incomplete outcome data, with three assessed as unclear and the remaining 10 studies as low risk.

3.3. Meta-analysis of blood pressure outcomes

A significant reduction in both SBP (WMD = −1.70 mmHg, 95 % CI = [−3.34, −0.06], $P = 0.04$, $I^2 = 45.4$ %) and DBP (WMD = −1.27

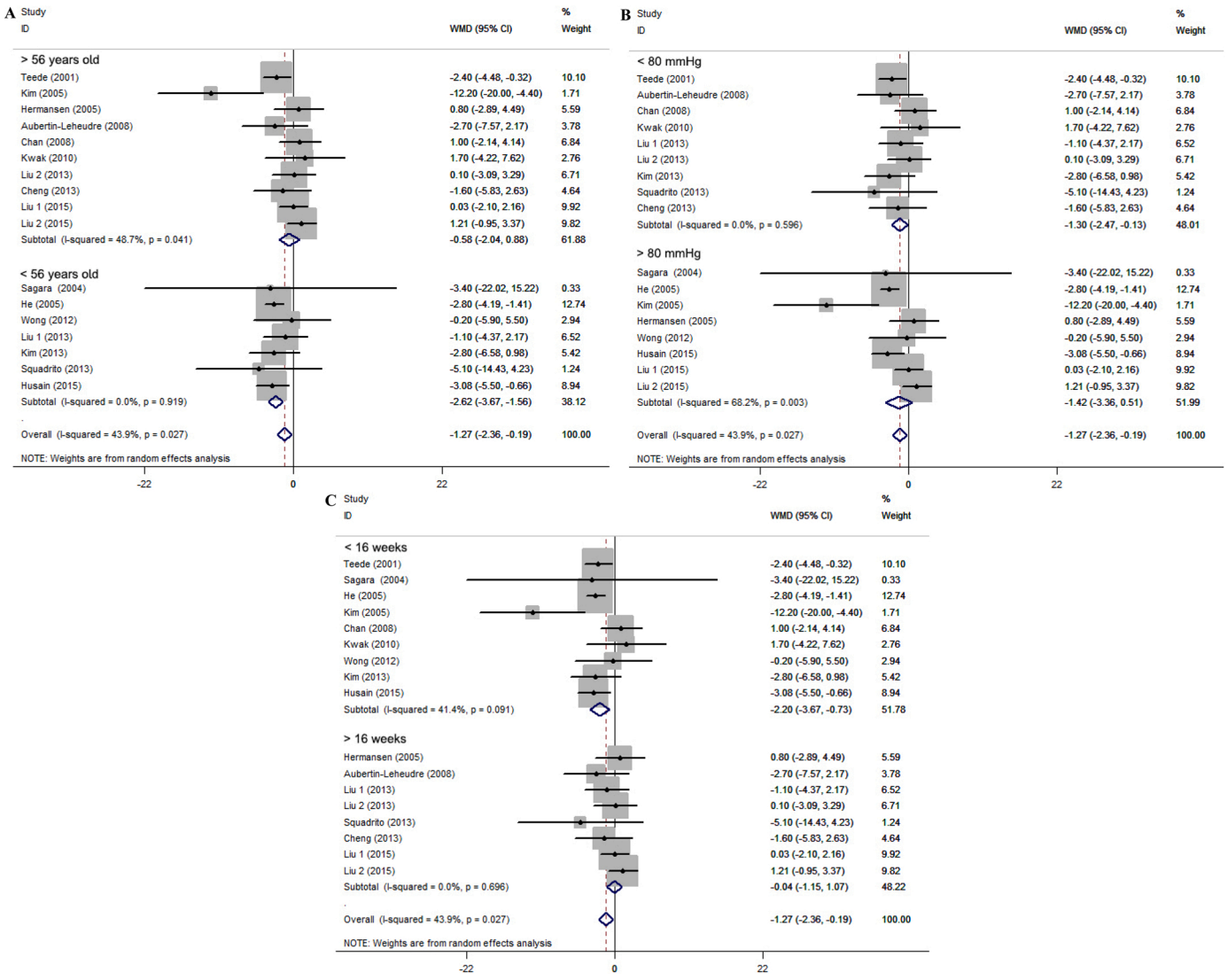

Fig. 4. Findings from subgroup analysis based on age (< 56, > 56 years old) (A), baseline blood pressure (< 130, > 130 mmHg) (B), duration (< 16, > 16 weeks) (C) and region (Asia, Europe, America) (D) regarding the effect of soy consumption on DBP.

mmHg, 95 % CI = [−2.36, -0.19], $P = 0.02$, $I^2 = 43.9$ %) were observed in the soy intake group when compared with controls (Fig. 2).

Subgroup analyses, identified a greater reduction in blood pressure for participants aged younger than 56 years (Fig. 3, A and Fig. 4, A) and lower baseline diastolic blood pressure (Fig. 4, B). In addition, both systolic (Fig. 3, C) and diastolic (Fig. 4, C) blood pressure were significantly reduced when soy intake duration was < 16 weeks.

3.4. Publication bias and sensitivity analysis

Egger's regression and Begg's rank-correlation tests indicated that there was no significant publication bias for SBP (P for Egger's test = 0.71 and Begg's test = 0.99) (Fig. 5, A) or DBP (P for Egger's test = 0.94 and Begg's test = 0.51) (Fig. 5, C). According to the findings from sensitivity analysis, pooled eff ;ect sizes obtained for the effect of soy intake on SBP (Fig. 5, B) and DBP (Fig. 5, D) were not sensitive to any particular study or group of studies.

4. Discussion

Data from 17 effect sizes were available to examine efficacy of soy consumption on blood pressure in adults. Our results showed that soy consumption significantly improves SBP and DBP. Subgroup analyses identified a greater reduction in blood pressure among younger participants with lower baseline diastolic blood pressure, and in trials lasting for < 16 weeks duration.

The effect of soy consumption on blood pressure has been previously assessed in several RCTs. A study by Washburn et al. indicated that 40 g of soy protein containing 68 mg of phytoestrogens, improved blood pressure abnormality.[39] In Teede et al., it was demonstrated that administration of 40 g of soy protein containing 118 mg of isoflavones, improved blood pressure in healthy men and women.[31] Furthermore, Welty et al. showed that a soy nut diet (containing 25 g of soy protein and 101 mg of aglycone isoflavones) lowered systolic blood pressure in hypertensive and normotensive patients [40]; whilst, Rivas et al. reported that a 3-month intervention with soymilk reduced blood pressure in men and women with mild-to-moderate hypertension, and that this hypotensive effect was related to urinary excretion of the isoflavonoid genistein.[41] Indeed, it has been shown that the BP-lowering effect of soy might be related to isoflavones,[42] the suspected active ingredients in soy, via the activation of endothelial nitric oxide (NO) synthase (eNOS) and stimulation of NO production. Genistein is one of the soy isoflavones that can result in activation of eNOS and NO synthesis.[43] This is confirmed in another study where it was demonstrated that higher soy

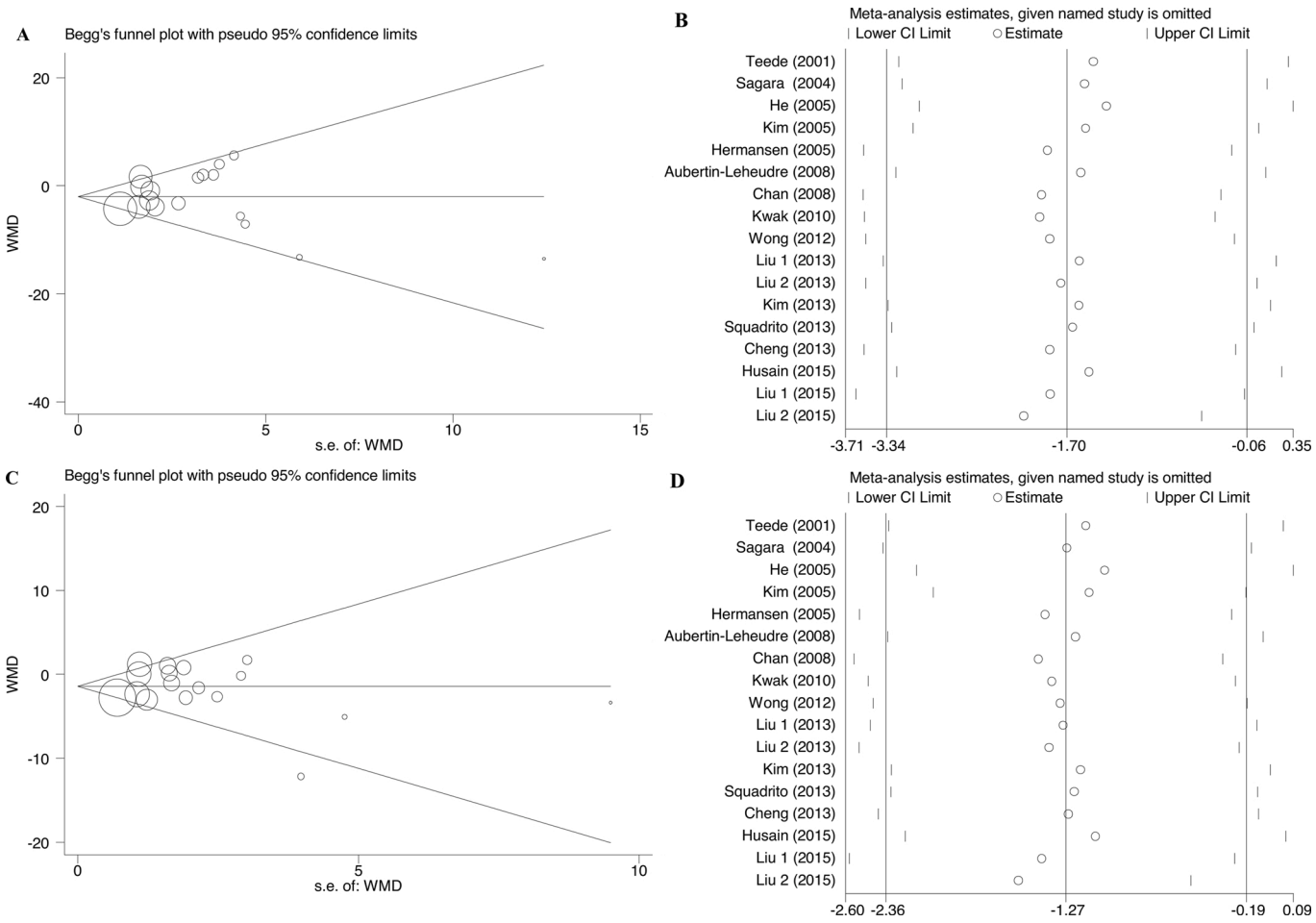

Fig. 5. The funnel plot and the result of sensitivity analysis for SBP (A, B) and DBP (C, D).

consumption is related to higher plasma concentrations of NO.[44]

It has been shown that oxidative stress and inflammation play a potential role in the development of hypertension [45]; thereby suggesting that soy isoflavones might lower BP through antioxidant and anti-inflammatory effects.[46,47] In line with the meta-analysis by Liu et al.,[48] it is unsurprising that we did not observe an inverse relationship of soy consumption with BP among older people, largely due to the adverse structural changes in the vessel wall among this group.[5] It is known that BP increases with enhancing arterial stiffness, concomitant to aging, and the consumption of phytoestrogens have been inversely related to arterial stiffness.[5] Moreover, soy consumption also reduces BP through its natriuretic effect, which is similar to furosemide.[13]

In the present study, we found that soy intake led to a higher reduction in blood pressure in participants with lower baseline systolic and diastolic BP, which is in contrast with result of the meta-analysis conducted by Liu et al[48] One reason that should be noted for this inconstancy is the difference in inclusion criteria regarding study design, inter-study heterogeneity, and risk of bias, which was lower across our pooled included studies.

4.1. Strengths and limitations

The present meta-analysis is the first comprehensive study to have assessed the influence of soy intake on BP from randomized double-blind placebo-controlled trials. We used a comprehensive and accurate systematic search strategy, that allowed us to examine both indexed and non-indexed trials. To reduce between-study heterogeneity and potential bias, and also enhance the power of results, we only included studies in which the control group received a placebo and where a double-blind design was employed. This approach improved quality of pooled analyses and subsequently permitting more rigorous insights in the effect of soy intake on BP. In addition, based on risk of bias assessment using Cochrane methodology, the quality of all studies was assessed overall as low risk. Subgroup analysis according to covariates that have clinical importance regarding soy intake and blood pressure improvements were pre-specified and provided additional insights to inform subsequent recommendations. It should be noted that there was no significant publication bias found, whilst pooled results were not sensitive to any individual study. Also, low amount of inter-study heterogeneity empowered the results. However, despite the clear novelty of this work, our study has some limitations that should be noted. First, as some included trials only reported dose of isoflavones, whilst others only reported soy, we were not able to apply a dose-response analysis. Second, we could not conduct subgroup analysis for baseline BMI and body weight of participants, which could be clinically important markers related to the change of BP, because of their absence in some included trials. Moreover, due to a variety of diseases among included study participants and lack of essential clinical data about their metabolic markers, we were not able to conduct additional subgroup analysis based on type of diseases and different health conditions without reducing the power of the analysis. Finally, although we contacted some corresponding authors to request missing essential data, in most cases, we received no response, or unsatisfactory responses.

4.2. Conclusion

In the present study, pooled effect sizes from 17 studies revealed a significant improvement in SBP and DBP in adults following soy consumption, in comparison with controls. In addition, subgroup analysis indicated a further reduction in both SBP and DBP in younger participants with lower baseline DBP and intervention durations < 16 weeks. Thus, increases to soy consumption could be considered as an alternative or complementary approach to improving BP outcomes among adults, and particularly among younger adults.

Authors contribution

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Funding

None.

Ethics approval and consent to participate

Not applicable.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgements

We thank Morteza Zare (https://www.researchgate.net/profile/Morteza_Zare), the expert statistician and head of Meta-Research Innovation office (METRIO), Shiraz University of Medical Sciences, Iran.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ctim.2021.102692.

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